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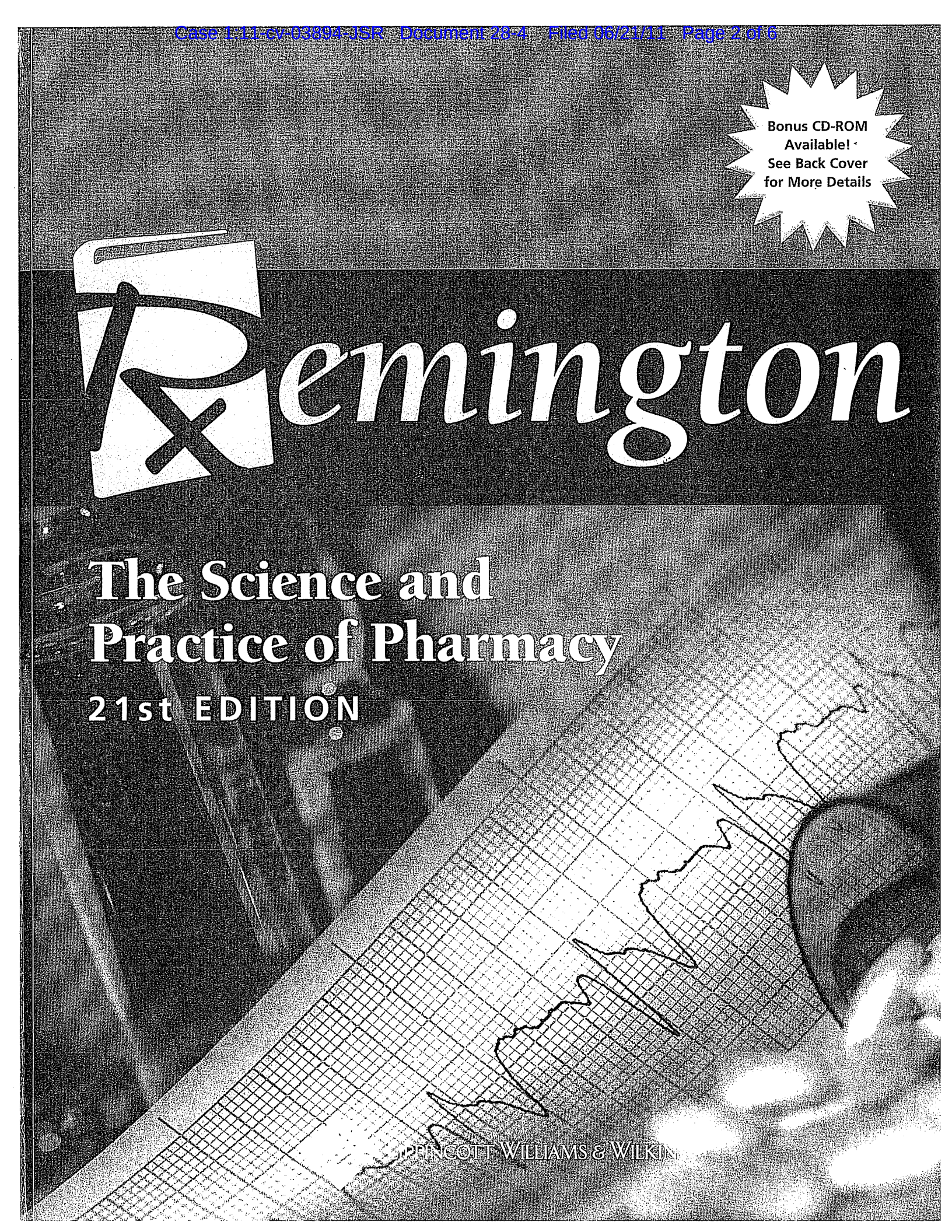

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$$\Delta G_{mix} = RT\,(n_s \ln \Phi_s + n_p \ln \Phi_p) + (n_s + N_p n_p)\, w \Phi_p\, \Phi_s \quad (32)$$

The first term on the right side of Equation 32 is the entropy of mixing, and the second term is the enthalpy of mixing. N_p in the second term is the degree of polymerization, and w is the effective molar interaction parameter (effectively, w is the square of the difference between solubility parameters of the polymer and solvent, multiplied by Avogadro's number). It is clear from the above equation that the value of ΔG_{mix} and therefore the polymer solubility are driven primarily by the volume fraction of the polymer in solution.

METHODS TO INCREASE SOLUBILITY OF POORLY SOLUBLE DRUGS

A large number of promising drug candidates do not make it to the market due to poor bioavailability, due primarily to their poor solubility in aqueous medium. Recently, several strategies have been used to improve solubility profile of these drugs. The strategies used to improve drug solubility include the following.

1. Use of buffers
2. Use of cosolvents
3. Surfactants
4. Complexation
5. Solid dispersions

USE OF BUFFERS—The idea behind use of buffers to improve solubility is to create and maintain pH conditions in a system that cause the drug to be in its ionized state. As discussed previously in this chapter, ionized fraction of a drug is much more soluble in water due to its increased polarity relative to the un-ionized fraction. Buffers can also help in reducing the likelihood of drug precipitation when drug solution is diluted in an aqueous medium. Consistent with the principles of solubility changes with pH, acidic drugs are formulated under relative basic conditions, while the opposite is true for the basic drugs. Some examples of drugs that are formulated with buffer systems are Amikacin sulfate (pH 3.5–5.5, citrate buffer) and Midazolam hydrochloride (pH 3).[17–19] The drugs that make good candidates for use of pH variation or buffers are the ones that have the ability to ionize within a pH range of 2–8.

USE OF COSOLVENTS—A common way to increase drug solubility is through the use of a water miscible organic solvent. This strategy is based on the fact that poor solubility of drugs in water results due to great difference in polarity of the two components, water being of very high polarity, and the drug having low polarity. Addition of a cosolvent with a polarity value of less than that of water reduces the difference between polarity of the drug and water-cosolvent system, thereby improving solubility. Commonly used cosolvents for this purpose are the hydrogen bonding organic solvents such as ethyl alcohol, propylene glycol and glycerin.

The polarity scale of solvents is defined by a property known as dielectric constant. This value for water is 80, and for ethyl alcohol, propylene glycol and glycerin, it is 24,032 and 42, respectively. Most poorly soluble drugs have dielectric constant values of less than 20. Examples of some parenteral solution that contain cosolvents include Chlordiazepoxide (25% propylene glycol), Diazepam (10% ethyl alcohol and 40% propylene glycol), and digoxin (10% ethyl alcohol and 40% propylene glycol). Non-polar and non-ionizable drugs are good candidates for cosolvent systems.[17–19]

SURFACTANTS—Surfactants are molecules with well defined polar and non-polar regions that allow them to aggregate in solution to form micelles. Non-polar drugs can partition into these micelles and be solubilized. Depending on the nature of the polar area, surfactants can be non-ionic (eg, polyethylene glycol), anionic (eg, sodium dodecyl sulfate), cationic (eg, trialkylammonium) and Zwitterionic (eg, glycine and proteins). Among these, the most commonly used ones are the anionic and non-ionic surfactants. Since the process of solubilization occurs due to presence of micelles, generally high concentrations of surfactants are needed to significantly improve drug solubility. One example of surfactant based solution is Taxol (paclitaxel), an anti-cancer drug that is solubilized in 50% solution of Cremophor. Other examples include Valrubicin in 50% Cremophor, and Cyclosporin in 65% Cremophor.[17–19]

COMPLEXATION—Complexation is the association between two or more molecules to form a noncovalent based complex that has higher solubility than the drug itself. From solubility standpoint, complexes can be put into two categories, stacking complexes and inclusion complexes. Stacking complexation is driven by association of nonpolar areas of the drug and complexing agent. This results in exclusion of the nonpolar areas from contact with water, thereby reducing total energy of the system. This aggregation is favored by large planar nonpolar regions on the molecules. Stacking can be homogeneous or mixed, but results in a clear solution.

Inclusion complexes are formed by insertion of drug molecule into a cavity formed by the complexing agent. In this arrangement, nonpolar area of the drug molecule is excluded from water due to its insertion in the complexing agent. One requirement for the complexing agent in such systems is that it has nonpolar core and polar exterior. The most commonly used inclusion complexing molecules are cyclodextrins. The cyclic oligomers of glucose are relatively soluble in water and have cavities large enough to accept nonpolar portions of many drug molecules. Cyclodextrins can consist of 6, 7, or 8 sugar residues and are classified as α, β, and γ, respectively. Due to geometric considerations, steroid molecules lend themselves very well for inclusion into cyclodextrin complexes.

SOLID DISPERSIONS—Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting-solvent method. It has also been defined as the product formed by converting a fluid drug-carrier combination to the solid state. The term co precipitate or co evaporate has also been used frequently used when a solid dispersion is prepared by solvent method.

Classification of Solid Dispersions—Solid dispersions can be classified as follows:

Simple eutectic mixtures
Solid solutions
Glass solutions of suspensions
Compound or complex formation between the drug and the carriers
Amorphous precipitations of drug in crystalline carrier

Simple Eutectic Mixtures—A simple eutectic mixture consists of two compounds that are completely miscible in the liquid state but only to a very limited extent in the solid state. A eutectic mixture of a sparingly water-soluble drug and a highly water-soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. These components are assumed to crystallize simultaneously in very small particulate sizes. The increase in specific surface area therefore, is mainly responsible for the increased rate of dissolution of a poorly water-soluble drug.

Differential thermal analysis (DTA) of binary mixtures normally exhibits two endotherms, but a binary mixture of eutectic composition usually exhibits a single major endotherm. In the case of a simple Eutectic system, the thaw points of binary mixtures of varying compositions are equal to the eutectic temperature of the system.

Solid Solutions—Solid solution consists of a solid solute dissolved in a solid solvent. The particle size in solid solution is reduced to molecular level. Successful solubilization of Itraconazole has been achieved using solid solution techniques. Solid solutions of lower drug concentrations generally give faster dissolution rate, and drug dissolution improves considerably with an increase in molecular weight of a water-soluble polymer such as polyethylene glycol.

Glass Solutions of Suspensions—A glass solution is a homogeneous system in which a glassy or a vitreous form of the carrier solubilizes drug molecules. PVP has been used as a carrier in several formulations. In its matrix PVP dissolved an organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

Compound or Complex Formation Between the Drug and the Carriers—This system is characterized by complexation of two compo-